OC 11.4: Phase 2/3 Trial of Subcutaneous Engineered FVIIa Marzeptacog Alfa (Activated) in Hemophilia A or B with Inhibitors: Efficacy, Safety and Pharmacokinetics

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Marzeptacog alfa (activated): MarzAA

Prophylaxis is not available for patients with hemophilia B with inhibitors or hemophilia A with inhibitors who fail emicizumab

- Four engineered amino acid substitutions within the FVIIa protein
- 9-fold more potent catalytic activity than NovoSeven RT
- Allows subcutaneous dosing
- Half-life prolonged when using subcutaneous dosing

Granted Orphan Drug Designation in the US and EU
MarzAA phase 2/3 SQ clinical trial MAA-201 design

- Patients with documented annual bleeding rate (ABR) >12
- Open label SQ study with individual dose escalation if needed in Hemophilia A or B with inhibitors

+ Primary endpoint: reduction in annualized bleed rate at final dose level
+ Secondary endpoints: safety and tolerability, inhibitor formation

Endpoint achieved if ABR decreases from ≥12 to ≤6
17 subjects were consented; 11 enrolled; 1 revoked consent before starting Part 2; 1 fatal SAE unrelated to MarzAA; 9 subjects completed the study.

Pre-treatment ABR: Mean 19.8; Range 12.2-26.7

Pre-treatment Proportion of Days with Bleeding (PDB): Mean 12.3%; Range 4-22%

Excellent compliance

- Total of 517 subcutaneous injections
- Exposure of 97 days of SQ dosing in one subject
- 7 subjects remained at 30 µg/kg while 2 subjects dose escalated to 60 µg/kg per protocol due to spontaneous bleeds

At the final dose level for all subjects:

- 7/9 subjects had zero bleeds (traumatic or spontaneous)
- Clinically and statistically significant reduction in ABR
- Clinically and statistically significant reduction in proportion of days with bleeding
MarzAA demonstrated robust reduction in annualized bleed rate (ABR)

<table>
<thead>
<tr>
<th>6-month recorded bleeds*</th>
<th>treatment period</th>
<th>30-day follow-up period</th>
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<tr>
<td>2680301  ABR=26.7</td>
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<td>2680302  ABR=18.3</td>
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<td>6430201  ABR=15.9</td>
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<td>0510101  ABR=22.2</td>
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<td>0510106  ABR=20.5</td>
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<td>6160101  ABR=24.3</td>
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*The width of each grey bar represents bleed duration: 1 to 9 days

Bleed

MarzAA: 30 µg/kg
MarzAA: 60 µg/kg

Preventive dosing for long walks

unrelated SAE
Significant reduction in ABR with treatment compared with baseline

**Median ABR reduced to zero**

- **2680301**
  - ABR=26.7
  - Zero at 60 µg/kg

- **2680302**
  - ABR=18.3
  - *unrelated SAE day 11

- **6430201**
  - ABR=15.9

- **6430202**
  - ABR=16.6

- **0510101**
  - ABR=22.2

- **6430203**
  - ABR=15.2

- **0510104**
  - ABR=21.2
  - Zero at 60 µg/kg

- **6430204**
  - ABR=15.9

- **0510106**
  - ABR=20.5

- **6160101**
  - ABR=24.3

**Annualized Bleed Rate:**
- Before treatment
- On MarzAA 30 µg/kg
- On MarzAA 60 µg/kg

**Annualized bleed rate**
- Median ABR overall reduced to zero at 60 µg/kg
Significant reduction in Proportion of Days with Bleeding (PDB)

Median Proportion of Days with Bleeding reduced to zero

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<tr>
<th>Subject</th>
<th>2680301</th>
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Grey denotes the Proportion of Days with Bleeding during period of observation

+ Average **pre-treatment** percentage of days of bleeding was **12.3%** (SD 5.8%) [median = 11.0%]
+ Average **on-treatment** percentage were reduced to **0.8%** (SD 0.9%) [median 0%]
+ Analysis of these pairwise differences by Wilcoxon signed-rank test has p=0.009 for 93.8% reduction
Marzeptacog alfa (activated) Phase 2 demonstrates clinical efficacy

Greater than 90% reduction in all bleeding; Median ABR zero; Median bleeding days zero

Mean Annualized Bleeding Rates (ABR) significantly reduced from 19.8 to 1.6
Mean Proportion of Days with Bleeding (PDB) significantly reduced from 12.3% to 0.8%
Safe & well tolerated, ~1% ISRs (517 SQ doses) and no ADAs
MAA-201 safety

Safe & well tolerated

+ No anti-drug antibodies were detected
+ One fatal unrelated SAE: intracerebral hemorrhage due to untreated hypertension
+ 517 SQ injections were administered
  - 6 injection site reactions in 2 subjects
    - 1 moderate swelling that resolved without sequelae in one subject
    - 2 mild and 3 moderate redness that resolved without sequelae in the other subject and did not occur with subsequent SQ injections
Mean First SQ dose PK; Mean Trough & Mean 7h post-dose FVIIa level by dose
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Conclusions on the marzeptacog alfa (activated) program

Moving forward in clinical development

- Clinical efficacy demonstrated
- Safe and well tolerated
- Moving forward with Phase 3 study planning
- No anti-drug antibodies detected
- Exploring the use of MarzAA in additional indications